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Sub-differentiating equivocal PI-RADS-3 lesions in multiparametric magnetic resonance imaging of the prostate to improve cancer detection.

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Highlights

- 1) Objective T2WI and DWI helped improve cancer yield for equivocal (PI-RADS 3) lesions
- 2) Biopsy recommendation improved PPV to 32% for GS 7-10 and 61% for any cancer
- 3) No-biopsy recommended had equivalent NPV to a negative MRI (PI-RADS 1-2) at 92%
- 4) The criteria-based score system could potentially avoid 48% of biopsies in the cohort

Abstract

Purpose

To evaluate sub-differentiation of PI-RADS-3 prostate lesions using pre-defined T2- and diffusion-weighted (DWI) MRI criteria, to aid the biopsy decision process.

Methods

143 patients with PIRADS-3 index lesions on MRI underwent targeted transperineal-MR/US fusion biopsy. Radiologists with 2 and 7-years experience performed blinded retrospective second-reads using set criteria and assigned biopsy recommendations. Inter-reader agreement, Gleason score (GS), positive (PPV) predictive values ($\pm 95\%$ confidence intervals) were calculated and compared by Fisher's exact test with Bonferroni-Hom correction.

Results

43% (61/143) patients had GS 6-10 and 21% (30/143) GS \geq 3+4 cancer. For peripheral zone lesions, significant differences in any cancer detection were found for shape (0.26 ± 0.13 geographical vs. 0.69 ± 0.23 rounded; $p=0.0055$) and ADC (mild 0.21 ± 0.12 vs marked 0.81 ± 0.19 ; $p=0.0001$). For transition zone, significantly increased cancer detection was shown for location (anterior 0.63 ± 0.15 vs. mid/posterior 0.31 ± 0.14 ; $p=0.0048$), border (pseudo-capsule 0.32 ± 0.14 vs. ill-defined 0.61 ± 0.15 ; $p=0.0092$), and ADC (mild 0.35 ± 0.12 vs marked restriction 0.68 ± 0.17 ; $p=0.0057$). Biopsy recommendations had 62% inter-reader agreement (89/143). Experienced reader PPVs were significantly higher for any cancer with "biopsy-recommended" 0.61 ± 0.11 vs. "no biopsy" 0.21 ± 0.10 ($p=0.0001$), and for GS 7-10 cancers: 0.32 ± 0.10 vs. 0.08 ± 0.07 , respectively ($p=0.0003$).

Conclusion

Identification of certain objective imaging criteria as well as a subjective biopsy

recommendation from an experienced radiologist can help to increase the predictive value of equivocal prostate lesions and inform the decision making process of whether or not to biopsy.

Abbreviations:

mpMRI = multiparametric Magnetic Resonance Imaging

PI-RADS = Prostate Imaging-Reporting and Data System

NPV = negative predictive value

PPV = positive predictive value

US = Ultrasound

T2WI = T2-weighted imaging

DWI = diffusion-weighted imaging

ADC = apparent diffusion coefficient

PSA = prostate specific antigen

GS = Gleason score

PZ = peripheral zone

TZ = transition zone

Keywords: Prostate MRI PIRADS Indeterminate

Introduction

Multiparametric prostate MRI (mpMRI) has become established in the diagnostic pathway of men with prostate cancer [1-3] and is now increasingly used in the pre-biopsy setting to allow selection of men with significant cancer for biopsy, while avoiding biopsy and unnecessary treatment in men without an MRI lesion [4,5].

The recently updated Prostate Imaging-Reporting and Data System (PI-RADS) guidelines are aimed at standardizing MRI acquisition and interpretation using a 5-point scoring system [6,7]. However, when MRI is being used to guide the clinical decision making process either in the context of a previous negative biopsy, or in biopsy naïve patients, this 5-point scale has to be translated into a binary decision of whether to biopsy or not. A PI-RADS score of 1-2 is considered a “negative” MRI, and has a >90% negative predictive value (NPV) for significant disease [8-9], thus biopsy can be reasonably avoided. Conversely, a PI-RADS 4-5 lesion is of high probability and targeted biopsy is warranted. An intermediate PI-RADS 3 lesion, however, straddles this decision making process, and biopsy in this case is under debate [10-12]. The overall detection of cancer in indeterminate lesions has been shown to vary from 6.5% - 60% for any cancer and 4.1% - 21% for significant cancer [10,13 -16]. This needs to be considered in the context of a “miss rate” of around 10% for a PIRADS score of 1-2. Importantly, detection rates have been shown to be higher in the peripheral zone [14] and as high as 40% in the context of a second-biopsy population [15], suggesting some PI-RADS 3 lesions deserve biopsy, whereas others could be safely deferred. Informing management of such lesions is particularly

relevant given the reported prevalence of indeterminate of 20.5– 26.3% using earlier Likert-based systems [10,16-18] is predicted to increase with a switch to using the PI-RADS-version 2 reporting system [19].

The aim of this study therefore was to evaluate if equivocal PI-RADS 3 lesions on mpMRI of the prostate can be further differentiated using pre-defined T2- and diffusion-weighted imaging (DWI) criteria, in order to aid in the biopsy decision process.

Materials and Methods

Study population

This single-institution retrospective study was part of an evaluation of transperineal prostate biopsies with the need for informed consent for data analysis waived by the local ethics committee. From January 2013 to April 2016, 155 consecutive patients with a dominant (index) lesion considered to be equivocal on mpMRI (PI-RADS 3) underwent transperineal prostate biopsies at our tertiary center. 4 patients were excluded due to hip replacements, 8 patients were excluded as their scans were performed on a 1.5T MRI scanner. Out of the remaining 143 patients, 35 had no previous prostate biopsies, 82 had previous negative systematic transrectal ultrasound (TRUS)-guided biopsies, and 26 were due for follow-up biopsy under active surveillance for Gleason score 6 cancer. The Standards of Reporting for MRI-

targeted Biopsy Studies (START) were used to describe the study population, the conduct and reporting of the MRI, and the conduct of the biopsy and the Standards of Reporting of Diagnostic Accuracy (STARD) were used to describe and discuss the results [20,21].

Magnetic resonance imaging

All patients underwent MRI on a 3-T scanner (HDx, GE Healthcare) using a 16-32 channel phased-array body coil. The MRI protocol included axial T1-weighted fast spin-echo (FSE) images of the pelvis and high-resolution T2-weighted fast recovery FSE images of the prostate in axial, sagittal, and coronal planes. T1-weighted imaging parameters were as follows: TR/TE, 561/11; flip angle, 70°; FOV, 24 × 24 cm; resolution 1.1 × 1.0. T2-weighted imaging parameters were as follows: TR/TE, 4273/102; FOV, 22 × 22 cm; resolution 0.8 × 0.7; 1.5 signal averages. Axial DWI was performed using a dual spin-echo planar imaging pulse sequence (TR/TE, 3775/70; FOV, 28 × 28 cm; resolution 2.2 × 2.2). A parallel imaging with array spatial sensitivity encoding technique was used with an acceleration factor of 2 to reduce image distortion, with 6 signal averages. The slice thickness for the axial T2-weighted and DWI sequences was 3 mm with 0-mm gap. Isotropic DW images were automatically obtained by combining images with three perpendicular diffusion axes, and b values of 150, 750, 1400 and 2000 s/mm² were acquired; apparent diffusion coefficient (ADC) maps were automatically calculated.

Image analysis

All mpMRI images were prospectively read at our center by one of two subspecialist body radiologists experienced in reading prostate MRI. T2WI and DWI sequences were prospectively evaluated using a Likert scale of tumor probability, based on the Prostate Imaging Reporting and Data System (PI-RADS v1) structured scoring criteria developed by the European Society of Urogenital Radiology (ESUR) [22] and a final score was defined by combining all scores for T2WI and DWI sequences as recommended in PI-RADS version 2 [23]. Equivocal “Likert 3” was taken to be equivalent to PI-RADS 3 and only the equivocal lesions were further analysed for this study. Two radiologists with 2 years (approximately 200 cases read) and 7 years (over 2,000 cases) years of experience performed a blinded retrospective second-read of each. In each case the readers were provided with the location of the lesion originally reported according to the PI-RADS sector map, in order to ensure the same lesion was re-assessed. Objective imaging criteria derived from PI-RADS descriptors were used to assess each lesion, along with topographical information such as anterior location of transition zone lesions or radial/parallel orientation of peripheral zone lesions [24-26]; table 1. The location of transition zone lesions was identified according to the sector map as originally reported and therefore inter-reader agreement was not assessed for this criterion. Finally, readers were asked to give a subjective binary recommendation whether or not to biopsy.

Biopsy

The Biopsee™ transperineal MRI/TRUS fusion biopsy system version 1 or 2

(Medcom, Darmstadt, Germany) was used for all biopsies. All patients had 18-24 systematic biopsies taken according to the Ginsburg protocol, using a spring-loaded biopsy gun with an 18 gauge needle [27]. 2 target biopsy cores were taken from each lesion before the systematic biopsies. In the systematic biopsy, 2 biopsy cores were sampled from each of 12 sectors, starting with the anterior sectors. All procedures were undertaken by 1 of 2 urologists with several years' experience of transperineal biopsy using the Biopsee™ MRI/TRUS fusion biopsy system.

Histopathology

All biopsies were reported by a specialist uropathologist and were reviewed a second time, by another uropathologist, prior to discussion at a multidisciplinary team meeting. Biopsies were reviewed according to the ISUP 2005 recommendations [28]. The final Gleason score (GS) was used as data for this study, with GS $\geq 3+4$ being considered as significant cancer.

Statistics

Inter-reader agreement and Kappa value with 95% Confidence Interval (CI) were calculated for each criterion. Gleason score 7-10 cancer detection rate, all cancer detection rate, and positive predictive values were calculated for each criterion, including targeted and systematic biopsy cores in the area that the index lesion was located in. For example: if an index lesion was called in the right anterior, the results for the targeted cores and the systematic cores in the right anterior were used for

analysis. Fisher's exact test in combination with Bonferroni-Holm correction and a p-value target alpha level of 0.05 was used to test for statistically significant difference of cancer proportions. The GraphPad QuickCalcs calculator software (GraphPad Software Inc. La Jolla, CA, USA) was used to calculate the respective p-values.

Results

59% (85/143) of index lesions were called in the transition zone and 41% (58/143) in the peripheral zone. At transperineal biopsy, 43% (61/143) patients had a GS 6-10 prostate cancer in the target area, 21% (30/143) patients had a $GS \geq 3+4$ cancer, and 6% (9/143) a $GS \geq 4+3$ cancer, resulting in an overall positive predictive value of 0.43 for any cancer and 0.21 for significant GS 7-10 cancer. The clinical characteristics are shown in Table 2. The PPV for each objective imaging criterion for either PZ or TZ lesions are shown in Tables 3-4. The results for the subjective biopsy recommendation are shown in Table 5.

Peripheral zone lesions

For peripheral zone (PZ) lesions, significant differences in cancer detection were found using the imaging criteria shape, DWI, and ADC. After Bonferroni-Holm correction for multiple comparisons, the criteria ADC and shape remained statistically significant for detection of any cancer, with ADC also being significant for detection of significant cancer. For wedge-shaped/geographical shape, PPV for detecting any cancer in the target area were 0.26 ± 0.13 compared to 0.69 ± 0.23 for round shape ($p=0.0055$, Kappa=0.466, CI 0.253 to 0.680). PPV was also higher for detection of GS 7-10 but the difference was not statistically significant ($p>0.05$). For a mildly reduced ADC, PPV for detecting any cancer in the target area was significantly lower for mild at 0.21 ± 0.12 compared to strong restriction at 0.81 ± 0.19

($p=0.0001$, Kappa=0.033, CI -0.017 to 0.083) and also lower for significant cancer, PPV 0.07 ± 0.08 vs. 0.56 ± 0.24 , respectively ($p=0.0002$).

Transition zone lesions

For transition zone (TZ) lesions, significant differences in cancer detection were found using the imaging criteria location, shape, border, homogeneity and ADC. After Bonferroni-Holm correction for multiple comparisons, the criteria location, border, and ADC remained statistically significant for detection of any cancer while the criterium border was also significant for detection of significant cancer. For mid/posterior location, the PPV for any cancer in the target area was significantly lower at 0.31 ± 0.14 compared to 0.63 ± 0.15 for an anterior location ($p=0.0048$). For pseudocapsule, PPV for any cancer in the target area were 0.32 ± 0.14 vs. 0.61 ± 0.15 ($p=0.0092$, Kappa=0.507, CI 0.326 to 0.689) for ill-defined border and 0.09 ± 0.08 vs. 0.34 ± 0.15 ($p=0.0071$), respectively for significant cancer. For a mildly reduced ADC, PPV for detecting any cancer in the target area were 0.35 ± 0.12 for mild vs 0.68 ± 0.17 ($p=0.0057$, Kappa=0.831, CI -0.006 to 0.168) for strong restriction, with PPV for significant cancer 0.14 ± 0.09 vs. 0.36 ± 0.18 , respectively ($p=0.0272$).

Biopsy Recommendation

When asked to make a subjective biopsy recommendation, agreement between the two readers was observed in 62.2% of cases (89/143, Kappa=0.263, 95% CI 0.118 to 0.407). PPVs for detecting any cancer in the target area for the experienced

reader were 0.21 ± 0.10 for “defer biopsy” vs. 0.61 ± 0.11 ($p=0.0001$) for “biopsy recommended” (**Figures 1-4**), with PPVs for significant cancer of 0.08 ± 0.07 vs. 0.32 ± 0.10 , respectively ($p=0.0003$). Even for a less experienced reader, this effect was significant, although not as pronounced, with a PPV for detecting any cancer of 0.35 ± 0.10 for “defer biopsy” vs. 0.57 ± 0.14 for “biopsy recommended” ($p=0.0133$) and PPV for significant cancer of 0.14 ± 0.07 vs. 0.35 ± 0.13 ($p=0.0050$), respectively (**Figure 5**).

Discussion

Our study shows that re-evaluation of equivocal MRI lesions by an experienced urologist, using only topographical, T2WI, and DWI and assessing set imaging criteria, improved diagnostic accuracy. Adding a subjective recommendation of whether or not to biopsy a lesion improved the cancer yield to 32% for GS 7-10 cancers and justified the “deserves biopsy” recommendation. Conversely the NPV of 0.92 for “avoid biopsy” lesions is equivalent to the NPV of a negative MRI (PI-RADS 1-2), which is effectively the reference standard for deferring biopsy. Even for a less experienced reader, this effect was found, although not as pronounced.

The overall PPV for an equivocal lesion was 43% for any cancer and 21% significant cancer, suggesting that the cancer detection rate in this group is too high to completely avoid biopsy. Rosenkrantz et al found detection rates of PI-RADS 3

lesions to be as high as 40% for any cancer and 14.5% for GS 7-10 in the context of a second-biopsy population, compared to lower detection rates in a biopsy-naïve population [15]. This needs to be taken into account when analyzing a mixed study population like ours and especially when undertaking a biopsy decision for an individual patient. Liddell et al. showed cancer detection rates to be generally lower at 6.5% in the PZ and 2.2% in the TZ [14], conversely we found higher detection rates in the TZ (48%) compared to PZ (38%), which may again reflect differences in the study populations.

A subjective biopsy recommendation requires reading experience and continuous feedback from biopsy results, therefore we also evaluated which individual imaging criteria are most useful to risk stratify equivocal prostate lesions. We found that for PZ lesions, the presence of round shape and low ADC significantly improved detection of any cancer, with a low ADC value yielding significantly higher rates of significant cancer. This is expected as DWI is the dominant sequence in the PZ, and shape is a key component of the scoring system in the PZ, particularly distinguishing a rounded (PI-RADS 4-5) versus ill-defined/geographical shape (PI-RADS 2).

Differentiation of other criteria on T2-weighted images such as location, border, T2 signal intensity, homogeneity and high DWI did not significantly improve cancer yield. For transition zone lesions, anterior location, ill-defined border, and low ADC yielded higher rates of cancer, with ill-defined borders also resulting in significantly higher rates of significant cancer detection. Again this is supportive of the PI-RADS system, where T2WI dominates and morphological features of a pseudocapsule or

homogeneous appearance reflect PI-RADS category 2 or 4 lesions, respectively. Interestingly, the use of the topographical information of anterior location helped further risk stratify TZ lesions, this is supportive of previous work [24] and could be considered in future iterations of the PI-RADS scoring system. Other criteria such as T2 signal intensity and DWI did not improve GS 7-10 cancer yield for transition zone lesions, the latter reflecting the secondary role played by DWI in the TZ. Inter-reader agreement for both DWI and ADC was noted to be lower than for other imaging criteria, which may reflect the selection bias of indeterminate PIRADS-3 lesions, i.e. cases with no or marked restricted diffusion are unlikely to be in the cohort. The results, however, lend further support to suggestions that future versions of PI-RADS state quantitative cut-offs or to use ADC ratios to help reduce subjectivity [26,29]. It should be noted that all lesions retrospectively analysed in this study were originally categorized as PI-RADS 3 and therefore likely exhibited the assessed criteria to a lower degree than lesions directly categorized as negative (PI-RADS 2) or suspicious (PI-RADS 4-5).

A strength of our study is the use of a targeted and a 24-core systematic transperineal biopsy approach as the reference standard. Limitations of this study are its retrospective analysis and the relatively small study population. As with any biopsy technique there is the potential for sampling error, for example leading to false negative results, however this is expected to be reduced with targeted compared to systematic biopsy. Although a prostatectomy cohort would offer more definitive histology, this would not include cases negative for cancer, and patients

with PI-RADS 3 lesions are less likely to undergo radical treatment. All lesions were prospectively called using the criteria and the Likert descriptor of 1-5 that was incorporated in PI-RADS version 1, wherein “Likert 3” there was taken to be equivalent to PI-RADS 3. For the retrospective analysis, the criteria definitions of PI-RADS version 2 along with topographical information such as anterior location of transition zone lesions or radial/parallel orientation of peripheral zone lesions were used. The initial classification as PI-RADS 3 may not have been correct in all cases, highlighting the value of double reading not only in a scientific but also a clinical setting. In addition, some lesions classified as intermediate probability using criteria from version 1 of the guidelines may be considered to be of PI-RADS 4 category using version 2 (**Figure 4.**). In this study, all initially intermediate lesions were re-read by an intermediately experienced (7 years) and a beginner (2 years) reader which again reflects clinical practice in many centres, few of which can provide a reader with more than 10 years of experience. This slightly limits the generalizability of our findings as reader studies addressing different levels of experience should ideally include 2 readers of each experience level. Dynamic contrast enhanced imaging was not used in all cases and therefore not evaluated, however, there is conflicting evidence to whether DCE is needed for prostate imaging, with some studies demonstrating a small benefit in the peripheral zone [30,31], whilst others have countered that inter-reader agreement for DCE is weak, especially in the peripheral zone [32] and added value is limited [33]. Recently, biparametric prostate MRI was found to offer a diagnostic accuracy and cancer detection rate equivalent to that of conventional full multiparametric contrast-

enhanced MR imaging protocols [34]. Our results offer an alternative to DCE by establishing that equivocal lesions, particularly in the peripheral zone, can be further differentiated by in-depth analysis of topography, T2WI, and DWI and a subjective biopsy recommendation given by an experienced radiologist.

Conclusions

Identification of certain objective imaging criteria as well as a subjective biopsy recommendation from an experienced radiologist can help to increase the predictive value of equivocal prostate lesions and inform the decision making process of whether or not to biopsy.

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Figures

Figure 1: PIRADS-3 lesion in the peripheral zone: biopsy not recommended

54 year old patient, PSA 5.72, MRI pre-biopsy. Wedge-shaped lesion (arrow) in the right base PZ which is not well demarcated on T2 (A), mild to moderately hypointense on ADC ($910 \times 10^{-6} \text{ mm}^2/\text{s}$) (B), and mildly hyperintense on DWI (C). Note PI-RADS-v1 criteria for DWI: category 3 as not otherwise meeting scores 2 or 4. “No biopsy” was recommended by both readers. Transperineal biopsy was negative with targeted cores in this region showing focal mild acute inflammation.

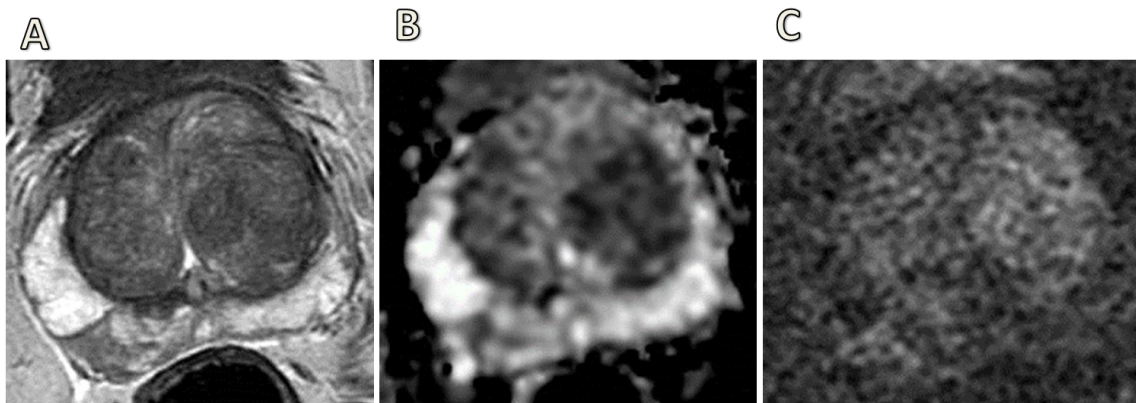


Figure 2: PIRADS-3 lesion in the peripheral zone: biopsy recommended

61 year old patient, PSA 5.94, MRI pre-biopsy. Linear lesion in the left apex PZ (arrows) on T2 (A), mildly hypointense on ADC ($1000 \times 10^{-6} \text{ mm}^2/\text{s}$) (B), and mildly hyperintense on DWI (C). Note PI-RADS-v1 criteria for DWI: category 3 as not otherwise meeting scores 2 or 4. “Biopsy recommended” was recorded for both

readers. Targeted transperineal biopsy in this region showed Gleason 3+3 in 25% of 1 of 2 cores, maximum core length 4 mm.

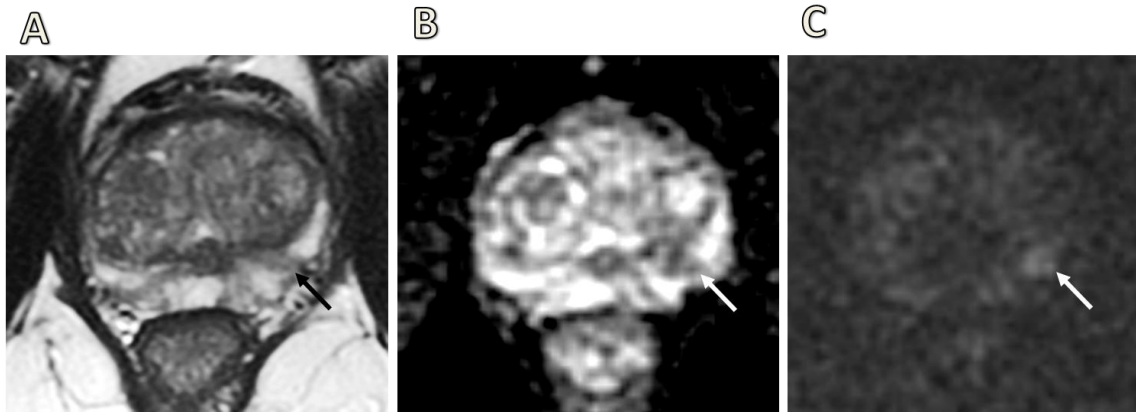


Figure 3: PIRADS-3 lesion in the transition zone: biopsy not recommended

73 year old patient, PSA 7.62, MRI pre-biopsy. Irregularly shaped PIRADS-3 lesion in the left base TZ (arrow) with heterogeneous signal intensity and obscured margins on T2WI (A), with markedly hypointense ADC ($760 \times 10^{-6} \text{ mm}^2/\text{s}$) (B), and mildly hyperintense DWI (C). Note PI-RADS-v2 criteria for T2: category 3 as not otherwise meeting scores 2 or 4. “No biopsy” was recommended by both readers.

Transperineal biopsy including target cores from this region was negative.

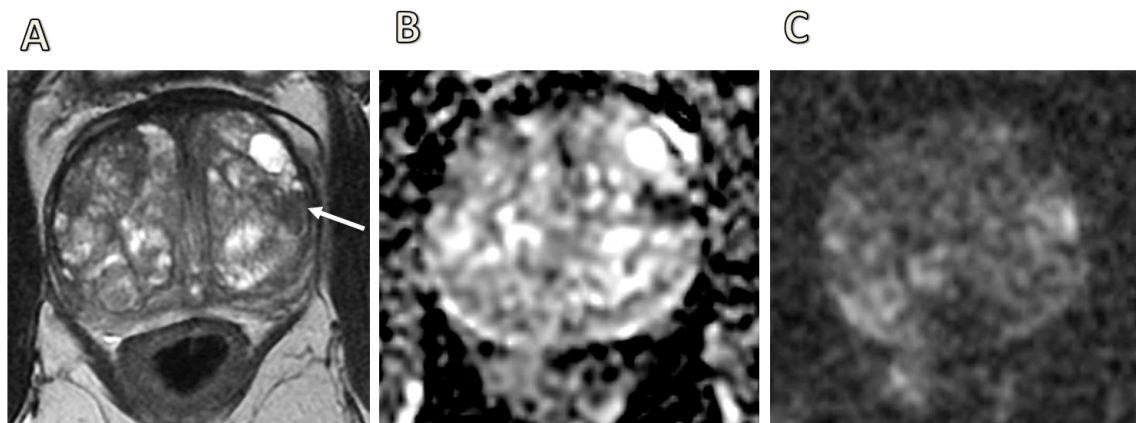
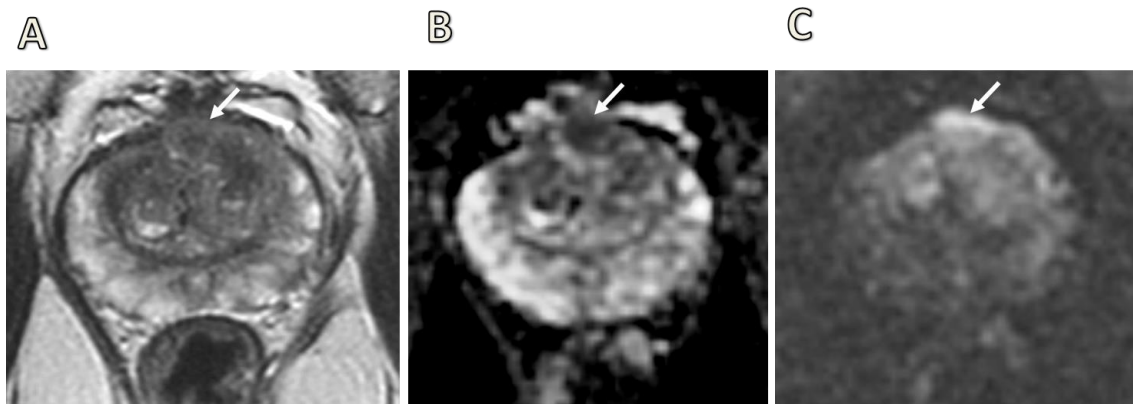


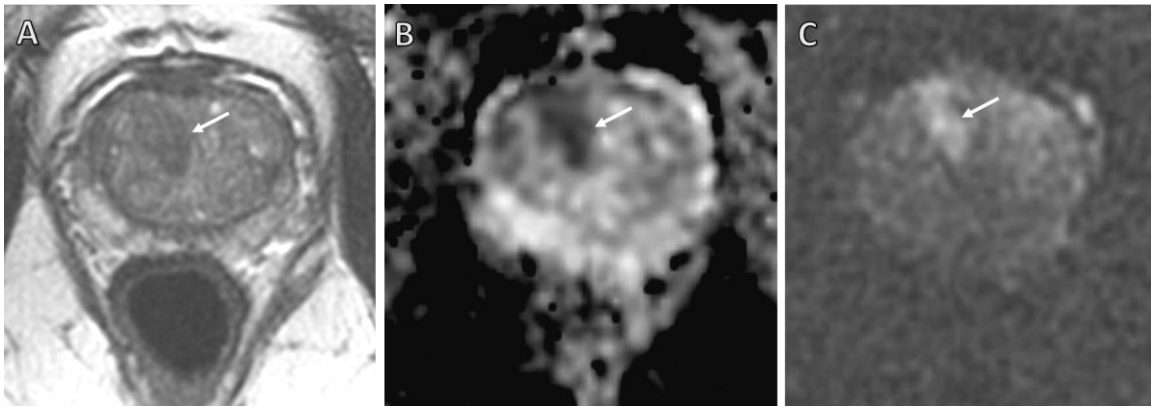
Figure 4: PIRADS-3 lesion in the transition zone: biopsy recommended

74 year old patient, PSA 8.44, MRI pre-biopsy. Lenticular PIRADS-3 lesion in the anterior midline midgland TZ (arrows) with ill-defined border and homogeneous signal intensity on T2WI (A), mildly hypointense ADC ($900 \times 10^{-6} \text{ mm}^2/\text{s}$) (B), and hyperintense DWI (C). Note the lesion was prospectively called indeterminate using PI-RADS-v1 criteria for T2: category 3 as not otherwise meeting scores 2 or 4. Using PI-RADS-v2 criteria for T2 the lesion is more appropriately “4” due to being lenticular, moderately hypointense (but $<1.5 \text{ cm}$ in greatest dimension). “Biopsy recommended” was recorded for both readers. Targeted transperineal biopsy in this region showed Gleason 3+4 (30% grade 4) in 40% of both cores, maximum core length 8 mm.

**Figure 5: PIRADS-3 lesion in the transition zone: reader disagreement**

67 year old patient, PSA 13.28, MRI pre-biopsy. Irregular-shaped PIRADS-3 lesion in the right mid TZ (arrows) with ill-defined border and mildly heterogeneous signal

intensity on T2WI (A), moderate restricted diffusion on ADC, value 857 (B) and b-2000 DWI (C). “Biopsy recommended” was recorded for experienced reader and “no biopsy” for junior reader. Targeted transperineal biopsy in this region showed Gleason 3+4 in 24% of both cores, maximum core length 5 mm.



Tables

Table 1: Imaging criteria used for reevaluation of PIRADS 3 lesions depending on location in peripheral and transition zone.

Feature	Peripheral zone lesions	Transition zone lesions
Location	Radial vs. Parallel to capsule	Mid / posterior vs. Anterior
Shape	Wedge vs. Round	Round vs. Irregular
Border	Ill vs. Well-defined	Pseudocapsule vs. Ill-defined
Signal intensity	Low vs. > Bladder wall	Low vs. > Bladder wall
Homogeneity	Heterogenous vs. Homogeneous	Heterogenous vs. Homogeneous
DWI	Normal / Iso vs. High Intensity	Normal / Iso vs. High Intensity
ADC	Normal / Mild vs. Low	Normal / Mild vs. Low

Table 2: Clinical characteristics of the patients included in the study. ¹

	Total n=143	IQR
Median Age [y]	65	58-69
Median PSA [ng/mL]	7.2	5.0-10.1
Median Volume [cc]	61	40-84
Median PSA Density [ng/mL/cm ³]	0.11	0.08-0.16
Cancer in target area	61 (43%)	
GS $\geq 3+4$ in target area	30 (21%)	
GS $\geq 4+3$ in target area	9 (6%)	

¹ Abbreviation: PSA = prostate-specific antigen. IQR = interquartile range.

Table 3: The positive (PPV) predictive values of different objective imaging criteria for peripheral zone lesions.²

Imaging criteria	description	Total [n]	% of total	GS 6-10 [n]	PPV	95% CI	p-value	GS 7-10 [n]	PPV	95% CI	p-value	Interrader Agreement	% of total
overall	overall	58	100%	22	0.38	±0.12		12	0.21	±0.10			
Location	radial	48	83%	16	0.33	±0.13	0.16	8	0.17	±0.11	0.19	24	41%
	parallel	10	17%	6	0.60	±0.30		4	0.40	±0.30			
Shape	geographical	42	72%	11	0.26	±0.13	0.005	7	0.17	±0.11	0.28	43	74%
	round	16	28%	11	0.69	±0.23		5	0.31	±0.23			
Border	Ill-defined	50	86%	18	0.36	±0.13	0.46	11	0.22	±0.11	1.00	39	67%

² Abbreviation: GS = Gleason score, PPV = positive predictive value, CI = Confidence intervall.

	Well-defined	8	14%	4	0.50	±0.35		1	0.13	±0.23			
T2 Signal intensity	< bladder	5	9%	2	0.40	±0.43	1.00	1	0.20	±0.35	1.00	51	88%
	> bladder	53	91%	20	0.38	±0.13		11	0.21	±0.11			
Homogeneity	Heterogeneous	36	62%	12	0.33	±0.15	0.41	8	0.22	±0.14	1.00	38	66%
	homogenous	22	38%	10	0.45	±0.21		4	0.18	±0.16			
DWI	Normal / Iso	44	76%	12	0.27	±0.13	0.047	7	0.16	±0.11	0.14	29	50%
	High Intensity	14	24%	10	0.71	±0.24		5	0.36	±0.25			
ADC	Normal / Mild	42	72%	9	0.21	±0.12	0.001	3	0.07	±0.08	0.0002	29	50%
	Low	16	28%	13	0.81	±0.19		9	0.56	±0.24			

Table 4: The positive (PPV) predictive values of different objective imaging criteria for transition zone lesions.³

Imaging criteria	description	Total [n]	% of total	GS 6-10 [n]	PPV	95% CI	p-value	GS 7-10 [n]	PPV	95% CI	p-value	Interrader Agreement	% of total
overall	overall	85	100%	39	0.46	±0.11		18	0.21	±0.09			
Location	Mid / Posterior	45	53%	14	0.31	±0.14	0.0048	6	0.13	±0.10	0.07	-	-
	Anterior	40	47%	25	0.63	±0.15		12	0.30	±0.14			
Shape	round	50	59%	17	0.34	±0.13	0.0145	7	0.14	±0.10	0.06	55	65%
	irregular	35	41%	22	0.63	±0.16		11	0.31	±0.15			
Border	Pseudocapsule	44	52%	14	0.32	±0.14	0.009	4	0.09	±0.08	0.007	64	75%

³ Abbreviation: GS = Gleason score, PPV = positive predictive value, CI = Confidence interval.

	Ill-defined	41	48%	25	0.61	±0.15	2	14	0.34	±0.15	1		
T2 Signal intensity	< bladder	8	9%	2	0.25	±0.30	0.28	1	0.13	±0.23	1.0	67	79%
	> bladder	77	91%	37	0.48	±0.11		17	0.22	±0.09			
Homogeneity	heterogenous	55	65	20	0.36	±0.13	0.023	8	0.15	±0.09	0.05	44	52%
	homogenous	30	35%	19	0.63	±0.17		10	0.33	±0.17			
DWI	Normal / Iso	55	65%	22	0.40	±0.13	0.17	9	0.16	±0.10	0.17	49	58%
	High Intensity	30	35%	17	0.57	±0.18		9	0.30	±0.16			
ADC	Normal / Mild	57	67%	20	0.35	±0.12	0.0057	8	0.14	±0.09	0.0272	40	47%
	Low	28	33%	19	0.68	±0.17		10	0.36	±0.18			

Table 5: The predictive value of a subjective binary recommendation by a subspecialist urologist whether or not to biopsy an equivocal multiparametric MRI lesion (PI-RADS 3) using a transperineal MRI/TRUS-fusion guided targeted and 18-24-core systematic prostate biopsy as the reference test.⁴

PI-RADS 3	Total [n]	% of total	GS 6- 10 [n]	PPV	95% CI	p- value	GS 7- 10 [n]	PPV	95% CI	p- value	Interreader Agreement	% of total
overall	143	100%	61	0.43	±0.08		30	0.21	±0.07			
<u>All lesions</u>												
Avoid biopsy	66	46%	14	0.21	±0.10	<0.01	5	0.08	±0.07	<0.01	89	62%
Biopsy recommended	77	54%	47	0.61	±0.11		25	0.32	±0.10			
<u>Peripheral zone</u>												
Avoid biopsy	18	31%	2	0.11	±0.14	<0.01	1	0.06	±0.11	0.08	30	52%

⁴ Abbreviation: GS = Gleason score, PPV = positive predictive value, CI = Confidence interval.

Biopsy recommended	40	69%	20	0.50	± 0.15		11	0.28	± 0.14	
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Transition zone

Avoid biopsy	48	56%	12	0.25	± 0.12	<0.01	4	0.08	± 0.08	<0.01	5 9	69%
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Biopsy recommended	37	44%	27	0.73	± 0.14		14	0.38	± 0.16	
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